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CHANGES IN ANTI-DIURETIC SUBSTANCE AFTER TOTAL PANCREATECTOMY

by

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INTRODUCTION

In 1913, v. d. VELDEN and FARINI injected the extract of the posterior lobe of the pituitary gland into a patient suffering from diabetes insipidus and succeeded in suppressing hyperdiuresis.

In 1923, FISHER showed that destruction of the dog's pituitary gland resulted in hyperdiuresis, which was, as he asserted, due to the lack of anti-diuretic substance (ADS) contained in the gland.

In 1937, GILMAN and GOODMAN made experiments on rats. The result was; in rats dehydration promoted secretion of ADS into the urine, while no amount of ADS was recognized in the urine of the rats whose pituitary glands had been extirpated. From this they inferred that ADS was nothing but anti-diuretic hormone (ADH) secreted from the pituitary.

SHIBUZAWA and others proved that secretion of ADS into the blood was promoted by surgical operation, anaesthesia, injury, dehydration, and other causes. According to them, a decrease in the amount of urine seen, for example, after an operation is due to the accelerated secretion of ADS.

It is generally accepted that the liver is a chief organ that has such a function to make ADS inactive that an impediment to general functioning of the liver necessarily disturbs the mechanism of inactivation of ADS, resulting in an increase in its amount in the serum.

On the other hand, when stained by the GOMORI's method, ADH can be detected, as dark blue granules in both the hypothalamus and the posterior lobe of the pituitary. BARGMAN avers that these granules are not ADH, but that their existence presupposes that of ADH, and that their disappearance from the organs means secretion, or transfer of ADH from these organs into the blood stream.

My previous experiment showed that a totally depancreatized dog developed a diabetic fatty liver due to the lack of insulin immediately after the operation. From other experiments hitherto made, it has been clear that total pancreatectomy exerts some influence upon the pituitary gland which is endocrinologically considered as an antagonistic organ concerning insulin. Especially, HASEGAWA in our clinic has histologically proved that total pancreatectomy lowers down the functional activity of the anterior lobe of the gland.

As is mentioned above, whether or not the early type of fatty liver occurs

after total pancreatectomy depends upon the amount of insulin administered, and the emaciation that follows total pancreatectomy is more marked when insulin lacks than otherwise.

The following experiments were made in order to see what influence administration of insulin after total pancreatectomy exerted upon the value of ADS in the serum, and the quantity of GOMORI's granules in both the hypothalamus and the posterior lobe of the pituitary gland.

RESULTS OF EXPERIMENT

A) Changes in the value of ADS in the serum

1) Method of measurement

BURN's method was applied. Pure-bred male rats, weighing 160gm to 180gm, were used for materials. They were chiefly given vegetables on the day before examination, and nothing but plenty of water on the day of examination. The experiments were performed on the afternoon of that day.

1cc of the serum to be tested was subcutaneously injected into the rats, and for the control group a physiologic saline solution was used. First, immediately after 5cc of water was put into the stomach through a *3 NELATON's catheter, the injection of the fluid to be tested (serum or saline solution) was performed. Next, the rats were separately put into a wire-mesh box. The box had a measuring cylinder set in its foot, into which was gathered the amount of urine the rat voided in the course of 2 hours. The percentage was then taken of the amount of urine thus gathered to that of water previously put into the stomach. Its high value implies a decrease in the amount of ADS in the serum to have been tested.

2) Results of experiment

i) Control group

As is shown in Table 1, the 7 cases into which a physiologic saline solution was injected evacuated about the same amount of urine, with 93 as average.

ii) Cases into which was injected the serum of the normal dog

Table 2 indicates that the average of the 4 cases is 75, and it seems that even an injection of normal serum can suppress urination.

Table. 1 Control group. (Rate of urination 2 hours after physiologic saline solution)

No. 1	96	93
No. 2	93	
No. 3	88	
No. 4	106	
No. 5	96	
No. 6	86	
No. 7	88	

Table. 2 Cases into which serum of normal dog was injected. (2 hours after injection)

No. 1	76	75
No. 2	68	
No. 3	72	
No. 4	85	

iii) Totally depancreatized dogs.

a) Cases given no insulin

As shown in Fig. 1, in all cases the level of ADS rose suddenly after the operation, reaching its highest point at the 6th to 24th hour, and returned nearly normal at the 72nd hour. It is well known that any kind of surgery brings about a temporary increase in the amount of ADS, and my present experiment showed no other changes worthy of special mention.

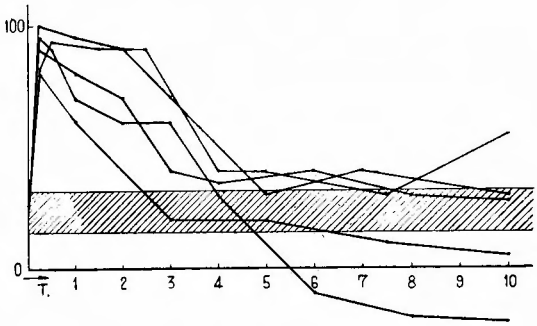

Fig. 1 Values of ADS in serum after total pancreatectomy. (Cases given no insulin)

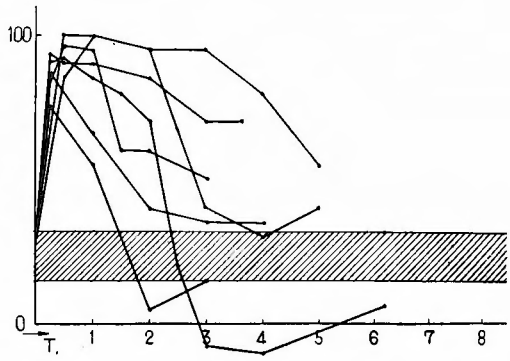

Fig. 2 Values of ADS in serum after total pancreatectomy. (Cases given insulin)

b) Cases given a large amount of insulin

The results of the 5 cases are given in Fig. 2. In all these cases, too, the level of ADS showed a temporary increase soon after the operation, but returned almost normal 3 or 4 days later.

From the results mentioned above it is clear that there is no striking difference between the two groups, that is, the insulin-treated group and the untreated group. According to Dr. YOSHIOKA, total pancreatectomy causes no increase in the value of ADS in the serum of the totally depancreatized dog, although it puts the animal into a highly dehydrated condition. On the basis of my experiment, however, this is not so clear as he asserts.

B) Histological findings

1) Method of experiment

Total pancreatectomy was performed on a certain number of dogs. After the operation some of them received a large amount of insulin, while the others did not. On the 5th postoperative day, all of them but one were killed through drawing their blood off by cutting the carotid artery under a slight anesthesia with 0.5% isomytal solution. The one exception was killed in the same way on the 14th day of administration. Upon their death, the hypothalamus and pituitary were taken out by craniotomy. As a control, normal dogs were killed and their same organs were taken out under the same condition.

The organs were first fixed in ZENKER's solution, next embedded in paraffin, and then sliced into about 6 micron pieces, which were stained by the GOMORI's method.

2) Results of experiment

Fig. 3 shows the posterior lobe of the pituitary of a normal dog, stained by

the GOMORI's method. There are a great many GOMORI's granules filling the tissue, and also many HERRING's Koerperchen filled with these granules. On the other hand, as in Figs. 4, 5 and 6, even in those cases whose pancreas was taken out there are very many GOMORI's granules filling the tissues of the two organs, no matter whether insulin was administered or not. In short, no remarkable difference can be made between the normal and the totally depancreatized dogs. Compared with Fig. 3 which shows a normal pituitary, Figs. 4 and 5 may give the impression that there are a little fewer GOMORI's granules in the totally depancreatized dog, regardless of administration of insulin, than in the normal one. Seen alone, however, Figs, 4 and 5 show many granules, and so it cannot be safely said that GOMORI's granules decreased as a direct result of the total pancreatectomy.

Fig. 7 shows the paraventricular nuclei of a normal dog, and Fig. 11 its supraoptic nuclei. Both are filled with GOMORI's granules, which implies the existence of an ample amount of ADS in the cells. Such is also the case with totally depancreatized dogs. It is impossible to ascertain a distinct difference between Figs. 7 and 11 which show the findings of normal dogs and Figs. 8, 9, 10, 12, 13, and 14, which show those of totally depancreatized dogs. Fig. 15 discloses the stalk of the pituitary as it appeared 5 days after the operation; there are many GOMORI's granules in the posterior lobe of the gland.

DISCUSSION AND CONCLUSION

My previous experiment confirmed that whether or not a totally depancreatized dog develop the early type of fatty liver depends upon the amount of insulin administered after the operation. In the present experiment, the measurement of ADH was taken in order to see what physiological changes would take place and how they would vary according to different amounts of insulin to be administered.

Total pancreatectomy causes a highly dehydrated condition and a fatty liver, which may well be expected to entail some changes in the value of ADS. So far as my present experiment is concerned, however, no such changes have been observed. The results are as follows; (1) Immediately after total pancreatectomy, the level of ADS in the serum rose suddenly, reaching its highest point at the 6th to 24th hour, and returned nearly normal about 3 days after the operation. The process was not affected by the administration of insulin. The rise was temporary and due to a transient promotion of secretion of ADS caused by the operation. There were observed no further changes peculiar to total pancreatectomy throughout the period of examination. Insulin made no striking difference, either.

(2) The findings of the hypothalamus and pituitary, both taken out 5 or 14 days after total pancreatectomy and stained by the GOMORI's method, revealed that in all cases, regardless of administration of insulin, there were a great many GOMORI's granules. No marked difference was observed between these findings and those of normal dogs.

(3) So far as my present experiment is concerned, no peculiar change was observed in ADS after total pancreatectomy. Administration of insulin made no striking difference, either.

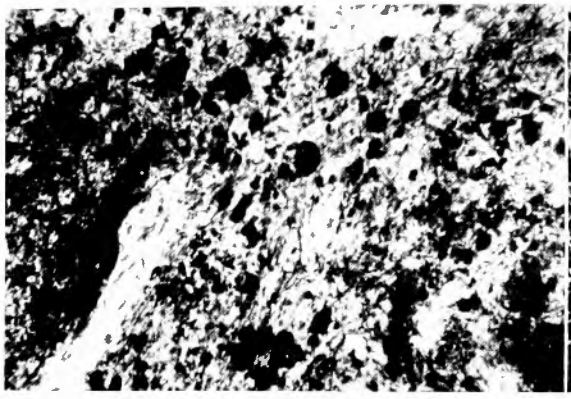

Fig. 3

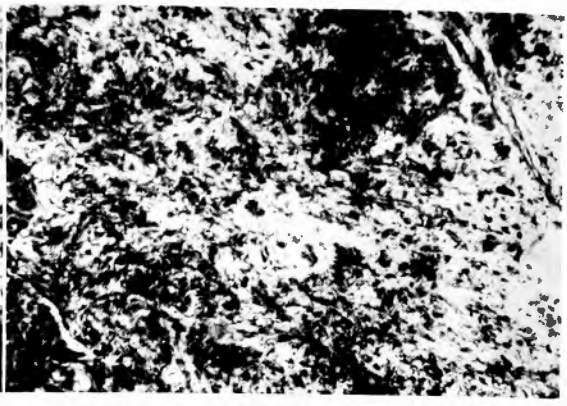

Fig. 4

Fig. 3 Microscopic appearance of normal pituitary. Gomori's stain. ×200

Fig. 4 Pituitary of totally depancratized dog given no insulin, seen 5 days after operation. Gomori's stain. ×200

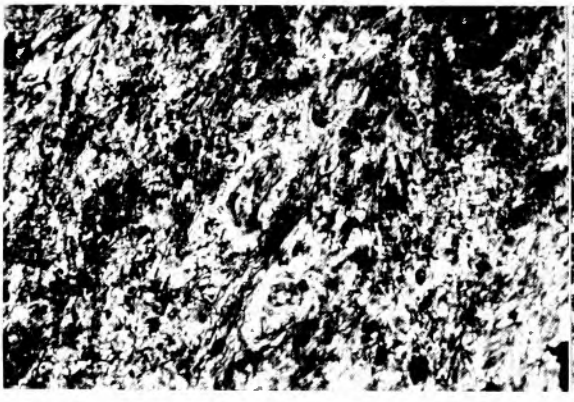

Fig. 5

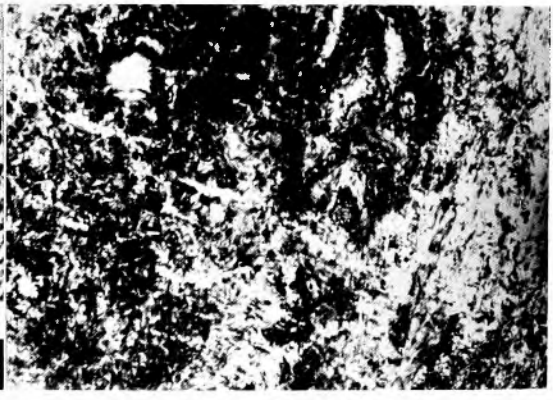

Fig. 6

Fig. 5 Pituitary of totally depancreatized dog given 3 u. per kg body weight of insulin. Photo taken 5 days after operation. Gomori's stain. ×200

Eig. 6 Pituitary of totally depancreatized dog given 3 u. per kg body weight of insulin, seen 14 days after operation. Gomori's stain. ×200

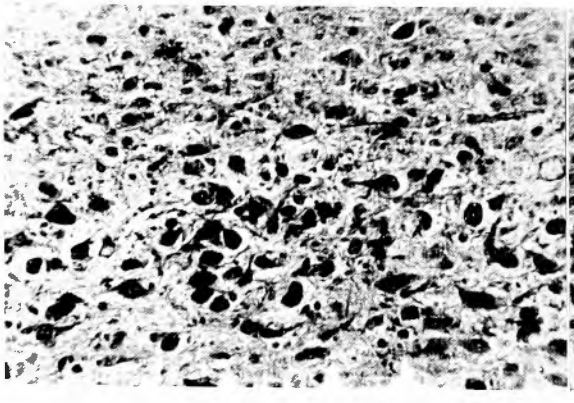

Fig. 7

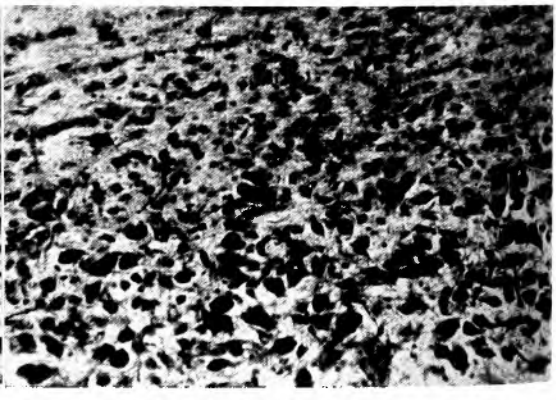

Fig. 8

Fig. 7 Normal paraventricular nuclei. Gomori's stain. ×200

Fig. 8 Paraventricular nuclei of depancreatized dog given no insulin, seen 5 days after operation.

Fig. 9

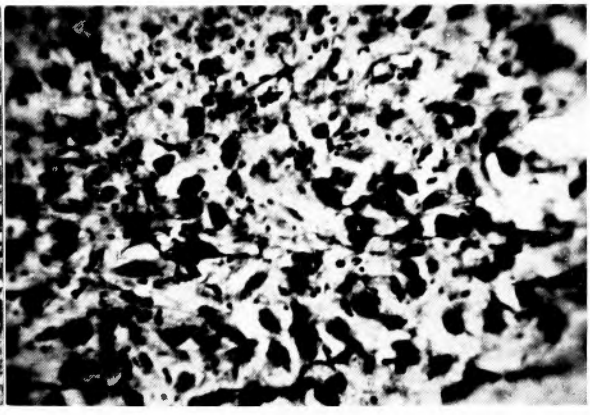

Fig. 10

Fig. 9 Paraventricular nuclei of depancreatized dog given 3 u. per kg body weight of insulin, seen on 5th postoperative day. Gomori's stain. ×200

Fig. 10 Paraventricular nuclei of depancreatized dog given 3 u. per kg body weight of insulin, seen on 14th postoperative day. Gomori's stain. ×200

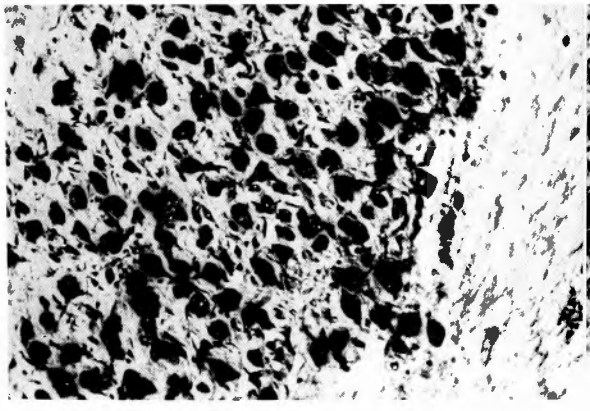

Fig. 11

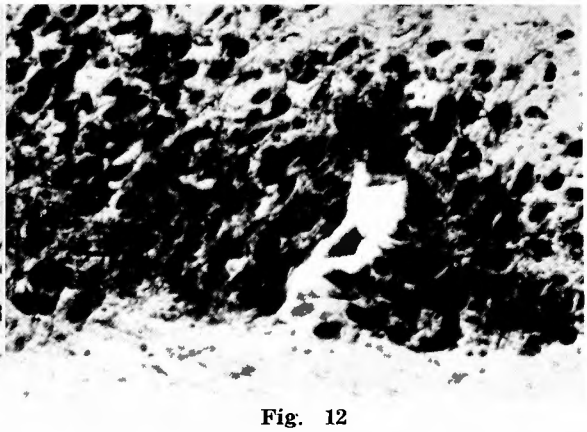

Fig. 12

Fig. 11 Normal supraoptic nuclei. Gomori's stain. ×200

Fig. 12 Supraoptic nuclei of depancreatized dog given no insulin. Photo taken 5 days after operation. Gomori's stain. ×200

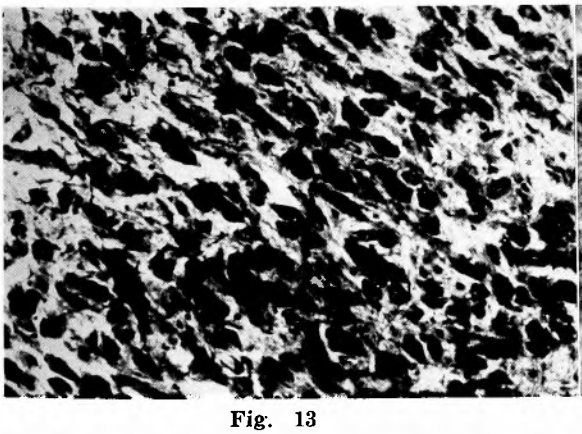

Fig. 13

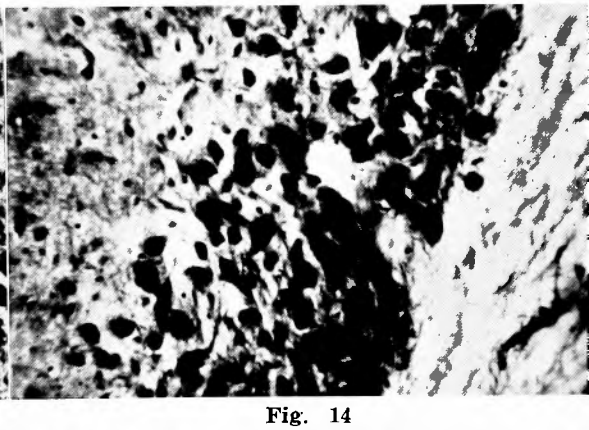

Fig. 14

Fig. 13 Supraoptic nuclei of depancreatized dog given 3 u. per kg body weight of insulin. Photo taken 5 days after operation. Gomori's stain. ×200

Fig. 14 Supraoptic nuclei of depancreatized dog given 3 u. per kg body weight of insulin. Photo taken 14 days after operation. Gomori's stain. ×200

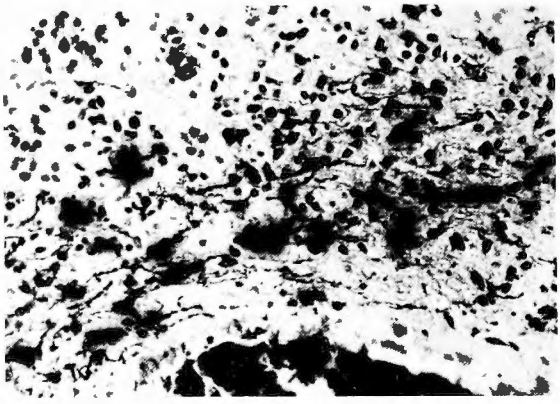

Fig. 15 Stalk of pituitary of depancreatized dog given no insulin, seen 5 days after operation. Gomori's stain. ×200

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5)……13) written in Japanese.

和 文 抄 録

膵臓全剔後の抗利尿物質（ADS）の変動

京都大学医学部外科学教室第1講座（指導 荒木千里教授）

押 谷 貞 亮

膵臓全剔後のインシュリン不足により，早期脂肪肝が発生し，衰弱を来たす事実を先の実験により確認したが，膵臓全剔後の生理学的変化の一端を知る目的で特にインシュリン投与群と無投与群に分け，血清ADS値を測定すると同時に，視床下部，脳下垂体後葉のGomori陽性物質の組織学的検索を行なつた．結果は次の如くで，脱水，脂肪肝発生，多尿等から予期した様な変化は得られなかつた．

1) 膵臓全剔後の血清ADS値は，術後インシュリン投与如何に拘らず直後より上昇し，6乃至24時間で最高値となり，3日頃より略正常値に戻る．これは手術の影響による一過性の分泌亢進で，以後の経過も膵剔特異の像は見られない．

2) 膵臓全剔後5日目及び14日目の視床下部及び脳下垂体後葉のGomori染色所見は，インシュリン投与の有無に拘らず，何れも，Gomori陽性物質を多量に包蔵し，正常犬と有意の差を認め難い．

3) 膵臓全剔後の術後ADSの変動は膵剔特異の所見を示さない．又インシュリン投与如何による有意の差も見られなかつた．